CLAIMS

1. A method for providing local analgesia, local anesthesia or nerve blockade in a human, comprising administering at a site in a human a formulation comprising a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid having free carboxylic acid end groups, said copolymer having a molecular weight of about 40 kDa to about 120kDa, said microspheres comprising from about 60% to about 85% bupivacaine free base, by weight, said microspheres being contained in a pharmaceutically acceptable medium for parenteral administration, said formulation having a concentration of bupivacaine free base from about 2.25 mg/ml to about 36.0 mg/ml and the formulation including a total amount of bupivacaine free base from about 45 mg to about 360 mg prior to administration, such that said formulation provides local analgesia, local anesthesia or nerve blockade at the site of administration less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration.

2. The method of claim 1, wherein said formulation further comprises an augmenting agent in an amount effective to prolong the effect of the local anesthetic for a time period greater than that obtained via administration of said formulation without said augmenting agent, such that the duration of local analgesia, local anesthesia or nerve blockade lasts for at least about 2 days after first administration.

3. The method of claim 1, wherein the duration of local analgesia is from about 2 to about 4 days after first administration.

4. The method of claim 1, wherein the duration of local analgesia is from about 4 to about 7 days after first administration.

5. The method of claim 1, wherein the level of local anesthetic at the site of administration is at least 150 times the level of local anesthetic in the systemic blood plasma.

6. The method of claim 1, wherein the formulation further comprises a concentration of dexamethasone from about 2.5 mcg/ml to about 10.0 mcg/ml.

7. The method of claim 1, wherein the microspheres further comprise 0.04% dexamethasone, by weight.

8. The method of claim 1, wherein the microspheres comprise about 72% bupivacaine base, by weight.

9. The method of claim 1, wherein the microspheres further comprise a polymer selected the group consisting of polyanhydrides, polyesters, polyorthoesters, proteins, and polysaccharides.

10. The method of claim 1, wherein the formulation provides an in-vitro dissolution of the local anesthetic from the biocompatible, biodegradable carrier under in-vitro conditions specified by the USP II Paddle Method, 100 RPM, 37 degrees Celsius, pH 3.0 in 900 ml of 10mM sodium phosphate buffer, as follows:

TIME (Hours)	Percent Release
0.25	about 2 to about 32
0.5	about 3 to about 60
1	about 6 to about 86
1.5	about 9 to about 92
2	about 12 to about 94
3	about 17 to about 97
4	about 23 to about 97

11. The method of claim 1, wherein the formulation provides an in-vitro dissolution of the local anesthetic from the biocompatible, biodegradable carrier under in-vitro conditions specified by the USP II Paddle Method, 100 RPM, 37 degrees Celsius, pH 3.0 in 900 ml of 10mM sodium phosphate buffer, as follows:

TIME (Hours)	Percent Release
1	From about 13 to about 36
2	From about 33 to about 65
4	From about 53 to about 87
8	From about 72 to about 95
12	From about 81 to about 98
18	From about 89 to about 100
24	From about 94 to about 100

12. The method of claim 1, wherein the formulation is administered perineurially.

13. The method of claim 1, wherein the formulation is administered subcutaneously.

14. The method claim 1, wherein the formulation is administered intramuscularly.

15. The method of claim 12, wherein the formulation provides an effect characterized by a mechanical pain detection threshold test in human patients in which the lowest number of the von Frey hair in which half of the stimulations produces a sensation of pain or unpleasantness is from about 16 to about 18 from about 2 to at least about 48 hours after administration, where the median baseline test is about 15.

16. The method of claim 12, wherein the formulation provides an effect characterized by a warm detection threshold test in which the median lowest increase in temperature from 32 C perceived by human patients, occurs at a temperature as follows in degrees C: about 40.5 to about 44.05 at 2 hours after administration; about 40.15 to about 44.85 at 4 hours after administration; about 40.15 to about 46.3 at 8 hours after administration; from about 41.7 to about 46.35 at 24 hours after administration; about 41.55 at 48 hours after administration; from about 40.4 to about 46.55 at 72 hours after administration; from about 41.1 to about 45.7 at 96 hours after administration; based on a median baseline test from about 39.9 to about 41.95.

17. The method of claim 12, wherein the formulation provides an effect characterized by perception of a temperature as painful, said temperature being at least 3°C greater than the temperature that is perceived as painful prior to administration of the formulation, having an onset of at least about 1 hour and a duration of at least about 2 days.

18. The method of claim 12, wherein the formulation provides an effect characterized by a mechanical pain response test in which human patients characterized the pain on stimulating the injected area 5 times with von Frey hair No. 17 on a Verbal Rank Scale of 0-10 where 0 = no pain and 10 = pain as bad as the patient could imagine, as follows, based on a median result for patients tested: about 1 at 2 hours after administration; about 1 at 4 hours after administration; about 1 at 8 hours after administration; from about 0 to about 0.5 at 24 hours after administration; from about 0 to about 0.5 at 48 hours after administration; from about 0 to about 1 at 72 hours after administration; from about 0 to about 1 at 96 hours after administration; and about 1 at 144 hours after administration, based on a median baseline test result of about 2.

19. The method of claim 1, wherein the administration is intercostally.

20. The method of claim 19, wherein the formulation provides an effect characterized by a pin prick pain response test in which the degree of pain was assessed by administering pin pricks in an area innervated by the intercostal nerve and assessed by O, 1 or 2 wherein O means the subject did not feel any pinpricks, 1 means the subject felt 2 or 3 pinpricks as touch or pressure and 2 means the subject felt 2 or 3 pinpricks as sharp, as follows, based on a mean result for patients tested: from about 1 to about 2 at 1 hour after administration; from about 0.5 to about 1.5 at 2 hours after administration; from 0 to about 1 at 6 hours after administration; from about 0 to about 0.75 at 24 hours after administration.

21. The method of claim 19, wherein the formulation provides an effect characterized by a numbness response test in which human patients characterized the numbness on stimulating the site of injection on a Verbal Rank Scale of 0-10 where 0 = not numb and 10 = totally numb, as follows, based on a mean result for patients tested: about 0 to about 4 at 2 hours after administration; about 0 to about 3 at 6 hours after administration; about 0 to about 2 at 12 hours and from 0 to about 2 at 24 hours.

22. The method of claim 19, wherein the mean Cmax of bupivacaine does not exceed 250 ng/mL, when administered intercostally.

23. The method of claim 22, wherein the mean Cmax of bupivacaine is from about 10 to about 20 ng/mL, when administered intercostally.

24. The method of claim 1, wherein the administration is at a single nerve and the local analgesia is measured by a pin prick response test in which the degree of pain was assessed by administering pin pricks in an area innervated by the superficial peroneal nerve and assessed by O, 1 or 2 wherein O means the subject did not feel any pinpricks (anesthesia), 1 means the subject felt 2 or 3 pinpricks as touch or pressure or felt one as touch or pressure and 1 as sharp (analgesia) and 2 means the subject felt 2 or 3 pinpricks as sharp.

25. The method of claim 1, wherein the administration is at a single nerve and wherein the maximum plasma bupivacaine concentration is less than about 25 ng/mL.

26. The method of claim 1, wherein the administration is at a single nerve and provides a effect characterized by a numbness response test in which human patients characterized the numbness on stimulating the site of injection on a Verbal Rank Scale of 0-10 where 0 = not numb and 10 = totally numb, as follows, based on a mean result for patients tested: about 0 to about 5 at 1 hours after administration; about 0 to about 4 at 6 hours after administration; about 0 to about 3 at 12 hours and from 0 to about 3 at 24 hours.

27. The method of claim 24, wherein the single nerve is the superficial peroneal nerve.

28. The method of claim 1, wherein the administration is to the superficial radial nerve

29. The method of claim 28, wherein the local analgesia is measured by a pin prick response test in which the degree of pain was assessed by administering pin pricks in an area innervated by the superficial radial nerve and assessed by O, 1 or 2 wherein O means the subject did not feel any pinpricks (anesthesia), 1 means the subject felt 2 or 3 pinpricks as touch or pressure or felt one as touch or pressure and 1 as sharp (analgesia) and 2 means the subject felt 2 or 3 pinpricks as sharp.

30. The method of claim 28, wherein the maximum plasma bupivacaine concentration is less than about 100 ng/mL.

31. The method of claim 28, wherein the formulation provides an effect characterized by a numbness response test in which human patients characterized the numbness on stimulating the site of injection on a Verbal Rank Scale of 0-10 where 0 = not numb and 10 = totally numb, as follows, based on a mean result for patients tested: about 0 to about 5 at 1 hours after administration; about 0 to about 4 at 6 hours after administration; about 0 to about 3 at 12 hours and from 0 to about 3 at 24 hours.

32. The method of claim 1, wherein the polymer has a viscosity from about 0.25 to about 0.42 dL/g.

33. A method for providing local analgesia, local anesthesia or nerve blockade in a human comprising administering at a site in a human a unit dose of microspheres comprising a biocompatible, biodegradable carrier and bupivacaine or a pharmaceutically acceptable salt thereof, effective to provide local analgesia, local anesthesia or nerve blockade at the site of administration in a human which occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration, wherein the mean Cmax of bupivacaine measured by microdialysis in the tissue at the site is from about 35,000 ng/ml to below a toxic concentration at the site and wherein a level of local anesthetic at the site of administration is at least 150 times the level of said local anesthetic which is absorbed systemically into blood plasma.

34. The method of claim 33, wherein said microspheres further comprises an effective amount of dexamethasone or a pharmaceutically acceptable salt thereof to prolong the effect of the bupivacaine for a time period greater than that obtained via administration of said formulation without said augmenting agent such that a duration of local analgesia, anesthesia or nerve blockade lasts for at least about 2 days after first administration, wherein the mean Cmax of dexamethasone measured by microdialysis in the tissue at the site is from about 45 ng/ml to below a toxic concentration at the site and wherein a level of augmenting agent at the site of administration is at least 250 times the level of augmenting agent absorbed systemically into blood plasma.

35. A method for providing local analgesia, local anesthesia or nerve blockade in a human, comprising administering a unit dose of microspheres comprising a biocompatible, biodegradable carrier and bupivacaine or a pharmaceutically acceptable salt thereof, effective to provide local analgesia, local anesthesia or nerve blockade at a site of administration in a human which occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration, wherein the mean Tmax of bupivacaine at the tissue at the site occurs at a time point from about 10 hours to about 45 hours after first administration.

36. The method of claim 35, wherein said microspheres further comprise an effective amount of dexamethasone or a pharmaceutically acceptable salt thereof to prolong the effect of the bupivacaine for a time period greater than that obtained via administration of said microspheres without said dexamethasone, such that a duration of local analgesia, anesthesia or nerve blockade lasts for at least about 2 days after first administration, wherein the mean Tmax of dexamathasone at the tissue at the site occurs at a time point from about 5 hours to about 40 hours after first administration..

37. The method of claim 33, wherein the mean AUCt of bupivacaine at 96 hours measured by microdialysis in the tissue at the site is from about 2,000,000 ng/ml*h to about 4,000,000 ng/ml*h.

38. The method of claim 37, wherein said microspheres further comprise an effective amount of dexamethasone or a pharmaceutically acceptable salt thereof to prolong the effect of the bupivacaine for a time period greater than that obtained via administration of said microspheres without said dexamethasone, such that a duration of local analgesia, anesthesia or nerve blockade lasts for at least about 2 days after first administration, wherein the mean AUCt of dexamethasone at 96 hours measured by microdialysis in the tissue at the site is from about 800 ng/ml*h to about 3,000 ng/ml*h.

39. The method of claim 33, wherein the mean Cmax of bupivacaine in the plasma is below about 250 ng/ml.

40. The method of claim 34, wherein the mean Cmax of dexamethasone in the plasma is below about 0.50 ng/ml.

41. The method of claim 35, wherein the mean Tmax of bupivicaine occurs at a time point from about 25 hours to about 50 hours after first administration.

42. The method of claim 35, wherein the mean Tmax of dexamethasone occurs at a time point from about 12 hours to about 30 hours after first administration..

43. The method of claim 33, wherein the mean AUCt of bupivacaine at 96 hours in the plasma is below about 12,000 ng/ml*h.

44. The method of claim 38, wherein the mean AUCt of dexamethasone at 96 hours in the plasma is below about 15 ng/ml*h.

45. The method of claim 33, wherein the formulation provides an effect characterized by a mean pin prick pain response test which is less than 1.0 at 3 hours after first administration.

46. The method of claim 33, wherein the formulation provides an effect characterized by a pin mean prick pain response test which is less than 1.0 at 24 hours after first administration.

47. The method of claim 33, wherein the formulation provides an effect characterized by a pin mean prick pain response test which is less than 1.0 at 48 hours after first administration.

48. The method of claim 33, wherein the formulation provides an effect characterized by a pin mean prick pain response test which is less than 1.0 at 72 hours after first administration.

49. The method of claim 33, wherein the formulation provides an effect characterized by a pin mean prick pain response test which is less than 1.0 at 96 hours after first administration.

50. The method of claims 33, wherein the formulation provides an effect characterized by a mean somesthetic response test which is less than 0.6 at 3 hours after first administration.

51. The method of claim 33, wherein the formulation provides an effect characterized by a mean somesthetic response test which is less than 0.6 at 24 hours after first administration.

52. The method of claim 33, wherein the formulation provides an effect characterized by a mean somesthetic response test which is less than 0.6 at 48 hours after first administration.

53. The method of claim 33, wherein the formulation provides an effect characterized by a mean somesthetic response test which is less than 0.6 at 72 hours after first administration.

54. The method of claim 33, wherein the formulation provides an effect characterized by a mean somesthetic response test which is less than 0.6 at 96 hours after first administration.

55. The method of claims 33, wherein the formulation provides an effect characterized by a mean warmth detection threshold result which is at least 3 degrees C over the baseline at 3 hours after first administration.

56. The method of claim 33, wherein the formulation provides an effect characterized by a mean warmth detection threshold result which is at least 3 degrees C over the baseline at 24 hours after first administration.

57. The method of claim 33, wherein the formulation provides an effect characterized by a mean warmth detection threshold result which is at least 3 degrees C over the baseline at 48 hours after first administration.

58. The method of claim 33, wherein the formulation provides an effect characterized by a mean warmth detection threshold result which is at least 3 degrees C over the baseline at 72 hours after first administration.

59. The method of claim 33, wherein the formulation provides an effect characterized by a mean warmth detection threshold result which is at least 3 degrees C over the baseline at 96 hours after first administration.

60. The method of claims 33, wherein the formulation provides an effect characterized by a mean warmth detection threshold result which is at least 3 degrees C over the baseline at 3 hours after first administration.

61. The method of claim 33, wherein the formulation provides an effect characterized by a mean heat pain detection threshold result which is at least 3 degrees C over the baseline at 24 hours after first administration.

62. The method of claim 33, wherein the formulation provides an effect characterized by a mean heat pain detection threshold result which is at least 3 degrees C over the baseline at 48 hours after first administration.

63. The method of claim 33, wherein the formulation provides an effect characterized by a mean heat pain detection threshold result which is at least 3 degrees C over the baseline at 72 hours after first administration.

64. The method of claim 33, wherein biocompatible, biodegradable carrier a copolymer of lactic acid and glycolic acid.

65. The method of claim 33, wherein the local anesthetic is bupivacaine free base.

66. The method of claim 33, wherein the local anesthetic is bupivacaine free base, the augmenting agent is dexamethasone, and the polymer is a copolymer of lactic and glycolic acid.

67. The method of claim 33, wherein the carrier comprises a polymer selected the group consisting of polyanhydrides, polyesters, copolymers of lactic acid and glycolic acid, polyorthoesters, proteins, and polysaccharides.

68. The method of claim 33, wherein the carrier is suspended in a pharmaceutically acceptable vehicle for injection.

69. A pharmaceutical formulation comprising a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid having free carboxylic acid end groups, said copolymer having a molecular weight of about 40 kDa to about 120kDa, said microspheres comprising from about 60% to about 85% bupivacaine free base, by weight, said microspheres being contained in a pharmaceutically acceptable medium for parenteral administration, such that the formulation has a concentration of bupivacaine free base from about 2.25 mg/ml to about 36.0 mg/ml and the formulation includes a total amount of bupivacaine free base from about 45 mg to about 360 mg prior to administration.

70. A unit dose pharmaceutical formulation suitable for parenteral administration to humans upon reconstitution with a pharmaceutically acceptable medium for parenteral administration comprising a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid having free carboxylic acid end groups, said copolymer a molecular weight of about 40 kDa to about 120kDa, said microspheres comprising from about 60% to about 85% bupivacaine free base, by weight, said microspheres including a total amount of bupivacaine free base from about 45 mg to about 360 mg prior to administration.

71. The formulation of claim 69, wherein the molecular weight of the polymer is about 40 kDa.

72. The formulation of claim 69, wherein the molecular weight of the polymer is about 120 kDa.

73. The formulation of claim 69, wherein the polymer has a viscosity from about 0.25 to about 0.42 dL/g.

74. The formulation of claim 69, wherein the microspheres are present in the medium in a concentration of about 6.25 mg/ml.

75. The formulation of claim 69, wherein the concentration of bupivacaine free base in said formulation is about 4.5 mg/ml.

76. The formulation of claim 69, wherein the microspheres are present in the medium in a concentration of about 12.5 mg/ml.

77. The formulation of claim 69, wherein the concentration of bupivacaine free base in said formulation is about 9.0 mg/ml.

78. The formulation of claim 69, wherein the microspheres are present in the medium in a concentration of about 25.0 mg/ml.

79. The formulation of claim 69, wherein the concentration of bupivacaine free base in said formulation is about 18.0 mg/ml.

80. The formulation of claim 69, further comprising dexamethasone in said formulation is about 2.5 mcg/ml to about 10.0 mcg/ml.

81. A method for providing local analgesia, local anesthesia or nerve blockade in a human, comprising administering at a site in a human a unit dose of microspheres comprising a biocompatible, biodegradable carrier and a local anesthetic, effective to provide local analgesia, local anesthesia or nerve blockade at the site of administration in a human which occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration, wherein the mean Cmax of local anesthetic measured by microdialysis in the tissue at the site is from a Cmax therapeutically equivalent to 35,000 ng/ml bupivicaine to below a toxic concentration at the site.

82. The method of claim 81, wherein said formulation further comprises an augmenting agent in an amount effective to prolong the effect of the local anesthetic for a time period greater than that obtained via administration of said formulation without said augmenting agent such that a duration of local analgesia lasts for at least about 2 days after first administration, wherein the level of augmenting agent at the site of administration is at least 250 times the level of augmenting agent in the blood plasma.

83. The method of claim 81, wherein said microspheres further comprises an effective amount of a cortocosteroid to prolong the effect of the local anesthetic for a time period greater than that obtained via administration of said formulation without said augmenting agent such that a duration of local analgesia, anesthesia or nerve blockade lasts for at least about 2 days after first administration, wherein the mean Cmax of corticosteroid measured by microdialysis in the tissue at the site is from a Cmax therapeutically equivalent to 45 ng/ml dexamethasone to below a toxic concentration at the site.

84. A method of detecting the local concentration of a local anesthetic at a site of administration comprising administering a local anesthetic at a site of a human and measuring the concentration of said local anesthetic in the tissue of said site by microdialysis at one or more time intervals.

85. A method of detecting the local concentration of a corticosteroid at a site of administration comprising administering a corticosteroid at a site of a human and measuring the concentration of said local anesthetic in the tissue of said site by microdialysis at one or more time intervals.

86. A method for preparing a local anesthetic formulation suitable for obtaining local analgesia, local anesthesia or nerve blockade in a human, comprising preparing a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid having free carboxylic acid end groups, said copolymer a molecular weight of about 40 kDa to about 120kDa, said microspheres comprising from about 60% to about 85% bupivacaine free base, by weight, and containing said microspheres in a pharmaceutically acceptable medium for parenteral administration, such that the formulation has a concentration of bupivacaine free base from about 2.25 mg/ml to about 36.0 mg/ml and the formulation includes a total amount of bupivacaine free base from about 45 mg to about 360 mg prior to administration.

87. The method of claim 1, wherein said microspheres are microcapsules.

88. The formulation of claim 69, wherein said microspheres are microcapsules.

89. A method for providing local analgesia, local anesthesia or nerve blockade in a human, comprising administering at a site in a human a formulation comprising a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid having free carboxylic acid end groups, said copolymer having a molecular weight of about 40 kDa to about 120kDa, said microspheres comprising from about 60% to about 85% bupivacaine free base, by weight, said microspheres being contained in a pharmaceutically acceptable medium for administration, said formulation having a concentration of bupivacaine free base from about 2.25 mg/ml to about 36.0 mg/ml and the formulation including a total amount of bupivacaine free base from about 45 mg to about 360 mg prior to administration, such that said formulation provides local analgesia, local anesthesia or nerve blockade at the site of administration less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration.

90. A pharmaceutical formulation comprising a unit dose of microspheres comprising a biocompatible, biodegradable carrier and bupivacaine or a pharmaceutically acceptable salt thereof, effective to provide local analgesia, local anesthesia or nerve blockade at the site of administration in a human which occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration, said formulation providing a mean Cmax of bupivacaine measured by microdialysis in the tissue at the site from about 35,000 ng/ml to below a toxic concentration at the site and a level of local anesthetic at the site of administration at least 150 times the level of said local anesthetic absorbed systemically into blood plasma.

91. The formulation of claim method of claim 90, wherein said microspheres further comprise an effective amount of dexamethasone or a pharmaceutically acceptable salt thereof to prolong the effect of the bupivacaine for a time period greater than that obtained via administration of said formulation without said augmenting agent such that a duration of local analgesia, anesthesia or nerve blockade lasts for at least about 2 days after first administration, said formulation providing a mean Cmax of dexamethasone measured by microdialysis in the tissue at the site from about 45 ng/ml to below a toxic concentration at the site and a level of augmenting agent at the site of administration at least 250 times the level of augmenting agent absorbed systemically into blood plasma.

92. A pharmaceutical formulation comprising a unit dose of microspheres comprising a biocompatible, biodegradable carrier and bupivacaine or a pharmaceutically acceptable salt thereof, effective to provide local analgesia, local anesthesia or nerve blockade at a site of administration in a human which occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration, said formulation providing a mean Tmax of bupivacaine at the tissue at the site occurs which occurs at a time point from about 10 hours to about 45 hours after first administration.

93. The formulation of claim 92, wherein said microspheres further comprise an effective amount of dexamethasone or a pharmaceutically acceptable salt thereof to prolong the effect of the bupivacaine for a time period greater than that obtained via administration of said microspheres without said dexamethasone, such that a duration of local analgesia, anesthesia or nerve blockade lasts for at least about 2 days after first administration, said formulation providing a mean Tmax of dexamathasone at the tissue at the site which occurs at a time point from about 5 hours to about 40 hours after first administration..